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RESEARCH ARTICLE

NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS FOR ALZHEIMER'S DISEASE: ADVANCES, CHALLENGES AND FUTURE PERSPECTIVES

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ABSTRACT

Alzheimer's disease (AD) is the most common form of dementia, characterized by progressive memory impairment, cognitive decline, and behavioral disturbances, and it represents a major public health challenge worldwide. Existing therapies, including cholinesterase inhibitors and N-methyl-D-aspartate receptor antagonists, provide only temporary symptomatic relief and do not modify the underlying disease mechanisms. Their effectiveness is further restricted by poor solubility, low bioavailability, systemic toxicity, and the protective nature of the blood–brain barrier (BBB), which prevents most drugs from reaching the brain. These limitations emphasize the urgent need for advanced delivery strategies. Nanotechnology has emerged as a promising approach to overcome these barriers. Engineered nano systems—such as liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, metallic nanoparticles, and nano micelles—offer enhanced solubility, improved pharmacokinetics, sustained release, and targeted transport across the BBB. Many of these carriers have also been adapted for theragnostic use, combining drug delivery with imaging functions to enable early diagnosis and personalized treatment. Preclinical investigations show that nanocarriers can enhance the stability and brain uptake of anti-Alzheimer's agents, reduce amyloid aggregation, and provide antioxidant and anti-inflammatory benefits. Despite encouraging progress, clinical translation remains limited due to challenges in large-scale production, regulatory approval, long-term safety evaluation, and economic feasibility. Addressing these barriers through international collaboration, harmonized standards, and integration of emerging fields such as RNA therapeutics and artificial intelligence may accelerate development. Overall, nanomedicine represents a transformative path toward disease-modifying interventions in AD.

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INTRODUCTION

Alzheimer's disease (AD) is a progressive, irreversible neurodegenerative disorder and the most frequent cause of dementia globally, contributing to 60–70% of cases (12). According to the World Health Organization (2023), more than 55 million people are currently living with dementia, and close to 10 million new cases are diagnosed each year (1). Clinically, AD is characterized by gradual memory impairment, language difficulties, mood and behavioral changes, and a steady decline in independence, making it one of the most pressing health challenges of the twenty-first century (12). With increasing life expectancy, the prevalence of AD is projected to rise, adding enormous medical, social, and economic strain worldwide. Current pharmacological interventions for AD remain limited. Cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, along with the N-methyl-D-aspartate (NMDA) receptor antagonist memantine, are routinely prescribed but provide only modest symptomatic benefits without halting the underlying neurodegeneration (2). More recently, amyloid-targeting monoclonal antibodies including aducanumab and lecanemab have been approved under accelerated pathways. However, their therapeutic impact remains debated due to restricted efficacy, high treatment costs, and adverse events such as cerebral edema and hemorrhage (3). These shortcomings highlight the urgent need for innovative therapeutic platforms that can address the multifactorial pathology of AD. One of the principal barriers to effective treatment is the blood–brain barrier (BBB), a specialized and selective structure that prevents toxins and pathogens from entering the brain but simultaneously blocks more than 98% of small-molecule drugs and nearly all biologics (6). Additional pharmacokinetic issues such as low solubility, poor bioavailability, and systemic toxicity further hinder conventional therapies. Consequently, many compounds that appear effective in preclinical studies fail during clinical trials.

Nanotechnology has emerged as a promising solution to these obstacles. By enabling nanoscale engineering of drug carriers, it offers improved stability, targeted delivery, sustained release, and reduced systemic side effects (7). Furthermore, nanomedicine allows the development of theranostic platforms, integrating treatment with diagnostic imaging, and holds potential for advancing personalized therapy in AD (8).
One of the most formidable challenges in developing effective AD therapies is the blood–brain barrier (BBB). The BBB is a highly selective and dynamic physiological barrier that protects the central nervous system (CNS) by preventing the entry of toxins and pathogens

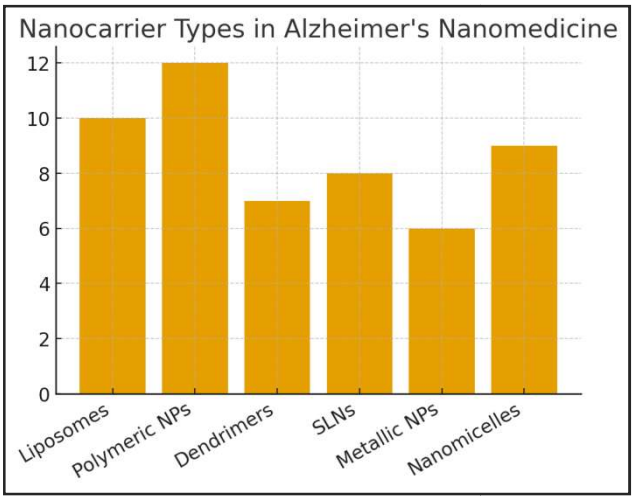

Figure 1. Nanocarrier Types in Alzheimer's Nanomedicine (5) (Liposomes, Polymeric NPs, Dendrimers, SLNs, Metallic NPs, Nanomicelles)

Therefore, it is critical to evaluate both the scientific progress and regulatory challenges associated with nanotechnology-based AD therapies. This review aims to provide a comprehensive assessment of recent advances in nanotechnology-enabled drug delivery systems for AD, while simultaneously highlighting regulatory frameworks that govern their development and approval. By integrating insights from both scientific and regulatory perspectives, this paper seeks to outline the opportunities and challenges for translating nanomedicine into effective clinical solutions for AD.

LITERATURE REVIEW

Table 1.

Author (Year)	Focus	Key Findings	Ref
Cummings et al. (2021)	AD drug development pipeline	Pipeline largely unsuccessful in late-stage trials; need novel strategies.	(2)
Li et al. (2021)	Gold nanoparticles theranostics	Theranostic potential; imaging + therapeutic delivery.	(4)
Wang et al. (2022)	Dendrimer-based strategies	Dendrimers inhibit amyloid aggregation; safety concerns remain.	(13)
Zhang et al. (2023)	Polymeric nanoparticles for siRNA	siRNA NPs reduced amyloid burden and improved cognition in models.	(11)
Jang et al. (2025)	Lipid-based nanoparticles (review)	Lipid NPs improve BBB transport and bioavailability; promising translational strategies.	(17)

MATERIALS AND METHODS

Types of Nanocarriers

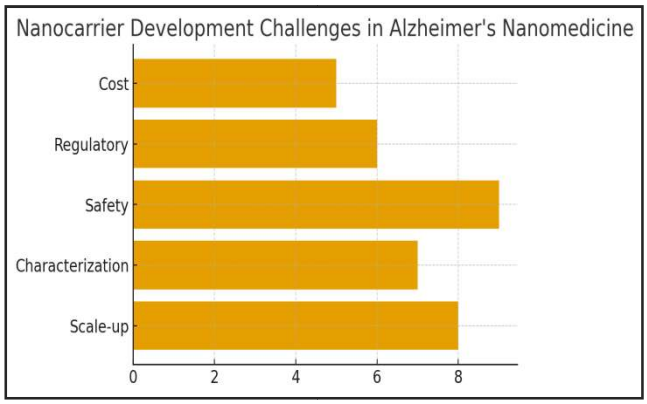

Figure 2. Nanocarrier Development Challenges in Alzheimer's Nanomedicine (10) (Scale-up, Characterization, Safety, Regulatory, Cost)

Liposomes: Liposomes are spherical vesicles made of phospholipid bilayers that can encapsulate both hydrophilic and hydrophobic drugs. Their biomimetic structure offers compatibility and reduced toxicity compared with synthetic carriers. Liposomal carriers of cholinesterase inhibitors and neuroprotective compounds have been shown to improve blood–brain barrier (BBB) penetration and prolong drug circulation. Functionalization with ligands such as transferrin and apolipoproteins further enhances receptor-mediated transport into the brain (8).

Polymeric Nanoparticles: Biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) have gained prominence for constructing nanoparticles that allow controlled and sustained release. Polymeric nanoparticles can be surface-modified with ligands, antibodies, or peptides to target amyloid-beta or tau pathology. Preclinical studies using siRNA-loaded polymeric nanoparticles have reported substantial reductions in amyloid burden and improvements in cognition in animal models (11).

Dendrimers: Dendrimers are synthetic, branched macromolecules with highly ordered structures and multiple terminal functional groups. Their unique design enables high drug-loading capacity and easy surface modification. In AD therapy, dendrimers conjugated with amyloid-binding moieties have demonstrated inhibition of plaque formation and facilitated clearance. However, concerns remain about long-term accumulation and cytotoxicity, which may limit their clinical application (13).

Solid Lipid Nanoparticles (SLNs): SLNs consist of a solid lipid core stabilized by surfactants, offering stability, controlled release, and compatibility with a wide range of drugs. These nanoparticles have been explored for encapsulating memantine and other neuroprotective agents, with evidence of improved BBB transport and enhanced neurocognitive outcomes in preclinical studies (14).

Metallic Nanoparticles: Metallic nanoparticles, such as gold and iron oxide formulations, provide additional diagnostic and therapeutic opportunities. Gold nanoparticles conjugated with amyloid antibodies have shown both therapeutic and

diagnostic potential, while iron oxide nanoparticles facilitate drug delivery alongside magnetic resonance imaging (MRI) monitoring of treatment distribution and disease progression. Despite these advantages, concerns about oxidative stress and potential genotoxicity limit their immediate clinical translation (4).

Nanomicelles: Nanomicelles are formed from amphiphilic molecules that self-assemble into nanosized structures. They are highly effective in improving the solubility of poorly water-soluble compounds such as curcumin and resveratrol. These molecules exhibit antioxidant and anti-inflammatory effects relevant to AD pathology. Nanomicelle formulations have shown improved stability and central nervous system (CNS) bioavailability, making them attractive candidates for clinical studies (15).

Methods

Mechanisms of Nanocarrier Action

Blood–Brain Barrier (BBB) Transport

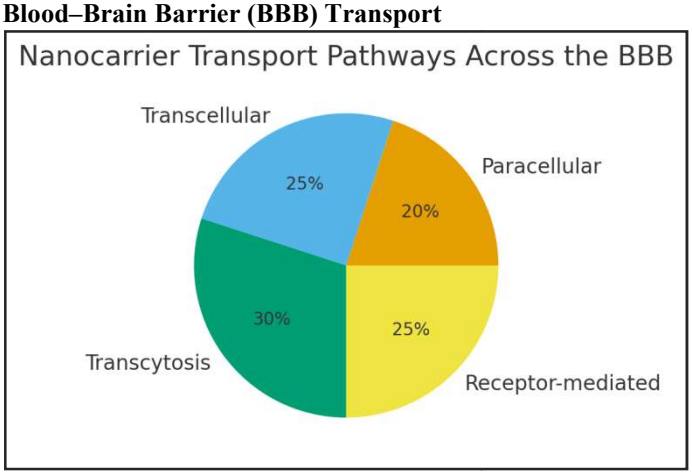

Figure 3. Nanocarrier Transport Pathways Across the BBB (10)

The BBB presents a significant obstacle to drug delivery in AD. Nanocarriers employ passive and active mechanisms to overcome this barrier. Passive transport takes advantage of the nanoscale size and lipophilic properties of carriers, enabling entry by diffusion or endocytosis. Liposomes and solid lipid nanoparticles are particularly effective in this regard. Active transport involves decorating nanocarrier surfaces with ligands such as transferrin, lactoferrin, or apolipoproteins, which bind to receptors on endothelial cells of the BBB. This receptor-mediated uptake significantly increases brain bioavailability compared with conventional formulations (7).

Amyloid- and Tau-Targeted Delivery: Nanocarriers can also be engineered to target disease hallmarks. For amyloid pathology, dendrimers and polymeric nanoparticles conjugated with amyloid-binding ligands inhibit plaque aggregation and facilitate clearance. Tau pathology is targeted using siRNA-loaded polymeric nanoparticles or antisense oligonucleotide delivery to suppress tau gene expression, reducing neurofibrillary tangle accumulation (11).

Antioxidant and Anti-inflammatory Delivery: Oxidative stress and neuroinflammation contribute significantly to AD progression. Nanocarriers encapsulating antioxidants such as curcumin and resveratrol have shown neuroprotective effects by mitigating oxidative damage and inflammatory responses. Polymeric nanoparticles and nanomicelles provide sustained release, ensuring longer neuroprotection and enhanced bioavailability in CNS tissues (15).

Regulatory and Translational Considerations: The methodology of evaluating nanomedicines is closely tied to regulatory expectations. Agencies such as the FDA, EMA, and Health Canada emphasize comprehensive physicochemical characterization, safety data, and reproducibility. Key domains include particle size, surface charge, morphology, and encapsulation efficiency; in vitro assays for cytotoxicity and BBB penetration; in vivo studies on biodistribution, clearance, and long-term toxicity; and clinical trials that confirm safety and efficacy in AD patients. One of the main barriers is the absence of harmonized international frameworks. Developers must often repeat studies to satisfy different agencies, resulting in duplication of effort, higher costs, and delayed approvals. Greater alignment of global standards and early regulatory engagement are essential to accelerate translation of nanotechnology into clinical practice (9). Nanotechnology presents a diverse set of tools for addressing the multifactorial pathology of AD. Liposomes and polymeric nanoparticles represent scalable and biocompatible options with the greatest near-term potential, while dendrimers, SLNs, metallic nanoparticles, and nanomicelles provide additional therapeutic and diagnostic opportunities. Mechanistic approaches focus on overcoming the BBB, targeting amyloid and tau pathology, and mitigating oxidative stress and inflammation. The regulatory landscape demands rigorous characterization and validation but lacks harmonization, which hampers progress. Overall, nanotechnology provides a scientifically promising but translationally challenging path toward more effective AD therapeutics.

RESULTS

Preclinical studies show improved BBB penetration and therapeutic gains using liposomes, PLGA nanoparticles, dendrimers, SLNs, and metallic NPs. Clinical studies remain limited; improved pharmacokinetics observed but robust efficacy not yet established.

Preclinical Findings: Nanocarriers in Alzheimer's Therapy: Recent preclinical studies highlight the effectiveness of nanotechnology-based drug delivery systems in enhancing drug penetration across the blood–brain barrier (BBB) and improving therapeutic efficacy in Alzheimer's disease (AD). Liposomes loaded with cholinesterase inhibitors such as donepezil and rivastigmine have demonstrated improved brain uptake and prolonged circulation times compared to free drug formulations. In rodent models, liposomal encapsulation reduced cognitive deficits and attenuated amyloid-beta (Aβ) plaque burden (8). Polymeric nanoparticles fabricated from biodegradable polymers like PLGA have been widely studied for targeted delivery. In murine AD models, PLGA nanoparticles carrying siRNA against amyloid precursor protein showed significant reduction in Aβ levels and improved learning ability (11). Polymeric nanocarriers have also been used to deliver antioxidants such as resveratrol and curcumin, demonstrating neuroprotective effects by reducing oxidative stress and mitochondrial dysfunction. Dendrimers functionalized with Aβ-binding ligands have shown remarkable potential in inhibiting plaque aggregation. Preclinical data indicate that dendrimer-based nanocarriers not

only prevent amyloid accumulation but also promote clearance via microglial activation, thereby improving synaptic function (13). Solid lipid nanoparticles (SLNs) encapsulating memantine have demonstrated enhanced BBB penetration and sustained release in rat models, leading to improved neurocognitive outcomes compared to free memantine (14).
Metallic nanoparticles, particularly gold and iron oxide, have been explored for theranostic purposes. Gold nanoparticles conjugated with Aβ antibodies exhibited both inhibitory and diagnostic potential in AD mouse models, while iron oxide nanoparticles facilitated MRI imaging alongside therapeutic delivery (4).

Clinical Findings: Translational Outcomes: Despite promising preclinical data, clinical translation remains limited. Only a handful of nanocarrier-based formulations for AD have advanced to early-phase human studies. Curcumin-loaded nanocarriers have been evaluated in Phase I/II clinical trials, showing improved bioavailability and safety but modest cognitive benefits. Larger, controlled trials are still lacking (15).

Lipid-based nanoparticles delivering cholinesterase inhibitors have reached preliminary clinical testing, demonstrating favorable pharmacokinetics compared to conventional oral formulations. However, efficacy outcomes remain inconclusive due to small sample sizes. Importantly, nanomedicines in other therapeutic areas, such as oncology and infectious diseases, have already achieved regulatory approval. Their success highlights the feasibility of nanocarriers but underscores the need for robust AD-specific trials.

Synthesis of Results: Preclinical studies consistently demonstrate that nanocarriers can overcome key barriers of conventional drug delivery in AD, including poor BBB penetration and systemic toxicity. Liposomes and polymeric nanoparticles show the greatest potential for clinical translation due to their scalability and safety. Dendrimers and metallic nanoparticles offer novel disease-modifying and diagnostic opportunities but face concerns about long-term toxicity. Clinical results remain sparse, with only limited trials demonstrating improved pharmacokinetics and safety. However, therapeutic efficacy data are inconclusive, underscoring the need for large, well-designed, randomized controlled trials. Overall, the results suggest that while nanotechnology is scientifically promising, its clinical validation in AD is still in its infancy.

DISCUSSION

- Liposomes & polymeric NPs: high translational potential (scalability, safety).
- Dendrimers & metallic NPs: innovative but safety/translatability concerns.
- Key barriers: regulatory harmonization, manufacturing scale-up, long-term safety data.

The findings from recent preclinical and early clinical studies demonstrate the enormous potential of nanotechnology-based drug delivery systems in addressing the long-standing therapeutic challenges of Alzheimer's disease (AD). However, a critical analysis of the results reveals a complex picture where scientific promise is often counterbalanced by translational and regulatory hurdles.

Comparative Performance of Nanocarriers: Liposomes and polymeric nanoparticles currently stand out as the most promising nanocarriers for AD due to their biocompatibility, established safety in other therapeutic areas, and scalability. Liposomes have demonstrated improved BBB penetration and sustained circulation times, which translate into higher brain uptake of cholinesterase inhibitors (8). Polymeric nanoparticles, particularly PLGA-based systems, offer precise control over drug release and enable functionalization with targeting ligands, making them highly adaptable platforms (11). In contrast, dendrimers provide unique advantages for amyloid-beta (Aβ) targeting due to their highly branched surface groups but raise concerns about long-term accumulation and potential toxicity (13). Solid lipid nanoparticles (SLNs) have the benefit of biocompatibility and sustained release but remain less explored clinically. Metallic nanoparticles, particularly gold and iron oxide, introduce opportunities for theranostics, combining diagnostic and therapeutic modalities. However, their safety profile remains under scrutiny, especially regarding immunogenicity and oxidative stress induction (4).

Translational Gap: Preclinical vs. Clinical: A major theme emerging from the results is the gap between preclinical efficacy and clinical validation. While animal studies consistently demonstrate reduced amyloid plaque load, improved cognitive performance, and enhanced drug bioavailability, human trials remain limited. The few clinical studies that exist have focused on nutraceuticals such as curcumin, which show bioavailability improvements but fail to demonstrate robust clinical efficacy (15). Several factors contribute to this translational gap. First, rodent models of AD often fail to capture the full complexity of human disease, including genetic, environmental, and comorbidity factors. Second, scaling up nanoparticle production from laboratory to GMP-compliant manufacturing introduces variability in size, charge, and surface functionalization that directly affect therapeutic outcomes. Finally, the long-term safety of nanosystems in humans remains poorly characterized, with concerns about biodistribution, immune activation, and organ accumulation (16).

Regulatory Challenges: Regulatory agencies recognize the promise of nanomedicine but continue to grapple with establishing harmonized frameworks for evaluation. The U.S. Food and Drug Administration (FDA) has issued guidance documents emphasizing detailed physicochemical characterization, stability studies, and robust safety data. The European Medicines Agency (EMA) has provided reflection papers highlighting concerns about immunogenicity and long-term toxicity. Health Canada has similarly introduced nanotechnology-specific guidance requiring evidence of reproducibility and risk–benefit analysis (7); (9). However, the lack of global consensus creates duplicative requirements across jurisdictions, delaying clinical translation. Furthermore, regulatory agencies demand extensive toxicological and pharmacokinetic data, which are costly and time-consuming to generate. Ethical concerns further complicate approval, including patient safety, informed consent for novel therapies, and ensuring equitable access once treatments are approved.

Safety and Ethical Considerations: One of the most critical unresolved issues is long-term safety. Nanoparticles may accumulate in the liver, spleen, and kidneys, leading to toxicity or immune reactions. Metallic nanoparticles, in particular, raise concerns about oxidative stress and potential genotoxicity (13). Ethical considerations include ensuring transparency in communicating risks to patients, protecting vulnerable populations such as elderly individuals with cognitive impairment, and balancing innovation with affordability. Another key ethical challenge is equitable access. Even if nanotechnology-enabled therapies prove effective, their high development costs may make them inaccessible in low- and middle-income countries, exacerbating global health inequalities. Policies ensuring affordability and equitable distribution will be critical for maximizing public health impact.

Opportunities for Future Development: Despite these challenges, nanotechnology offers several opportunities for advancing AD therapy. Personalized nanomedicine, where drug formulations are tailored to an individual's genetic and biomarker profile, could enhance therapeutic efficacy while minimizing toxicity. Combining nanotechnology with other emerging fields, such as RNA therapeutics and CRISPR-based gene editing, may unlock synergistic approaches for disease modification. Furthermore, artificial intelligence (AI) and machine learning can optimize nanocarrier design, predict safety outcomes, and accelerate the drug discovery process (7). Theranostic nanocarriers represent another promising frontier. By combining imaging and therapeutic functions, they could enable early diagnosis, real-time monitoring of treatment response, and personalized dosing strategies. While still in preclinical stages, theranostic approaches highlight the versatility of nanotechnology in addressing multiple unmet needs simultaneously.

CONCLUSION

Nanocarriers offer promising strategies to overcome BBB and target AD pathology. Priorities: large clinical trials, harmonized regulatory pathways, and long-term safety evaluations. Alzheimer's disease (AD) continues to represent one of the greatest unmet medical challenges of the twenty-first century, with its rising prevalence imposing profound clinical, social, and economic burdens globally. Despite substantial research efforts, current therapeutic options remain limited to symptomatic management, failing to halt or reverse neurodegeneration. Conventional pharmacological strategies are further constrained by poor bioavailability, systemic side effects, and the formidable obstacle of the blood–brain barrier (BBB). Against this backdrop, nanotechnology-based drug delivery systems have emerged as a transformative platform with the potential to reshape the therapeutic landscape of AD.

This review highlights that a diverse range of nanocarriers—including liposomes, polymeric nanoparticles, dendrimers, nanomicelles, solid lipid nanoparticles (SLNs), and metallic nanoparticles—offer innovative strategies to overcome the limitations of conventional therapies. Preclinical studies consistently demonstrate that these systems enhance BBB penetration, improve pharmacokinetics, and allow targeted delivery to amyloid and tau pathologies. Among them, liposomes and polymeric nanoparticles currently appear most promising for clinical translation due to their established safety, scalability, and adaptability. Dendrimers, SLNs, and metallic nanoparticles provide unique mechanistic advantages, including amyloid aggregation inhibition and theranostic capabilities, though they face greater concerns regarding long-term safety and reproducibility (8); (11). While the scientific potential of nanomedicine is evident, clinical translation in AD remains in its infancy. Only limited human trials have been conducted, with curcumin-loaded nanocarriers and lipid-based nanoparticles demonstrating improved bioavailability and safety but failing to establish robust cognitive benefits (15). The persistent translational gap underscores the challenges of extrapolating results from preclinical animal models, which often inadequately replicate the complexity of human AD. Moreover, issues of manufacturing scalability, GMP compliance, and variability in physicochemical properties further hinder clinical progress (9).From a regulatory perspective, the development of nanomedicine for AD is complicated by the lack of harmonized global frameworks. Regulatory agencies such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and Health Canada have introduced guidance documents addressing quality, safety, and efficacy evaluation. Yet, significant challenges remain, particularly regarding the long-term safety assessment, immunogenicity, and classification of nanomedicines. The absence of consensus across jurisdictions leads to duplicative requirements, delays in development, and uncertainty for sponsors (7). Addressing these regulatory complexities will require international collaboration, harmonized standards, and greater integration of regulatory science into early-stage nanomedicine development.

Ethical and safety considerations also demand careful attention. Nanoparticles have the potential to accumulate in off-target organs such as the liver and spleen, raising concerns about chronic toxicity and immune activation. Metallic nanoparticles, in particular, carry risks of oxidative stress and potential genotoxicity (13). Ethical issues extend beyond safety to encompass informed consent in vulnerable populations, transparency in communicating risks, and equitable access to therapies. Given the high cost of nanomedicine development, there is a risk that successful treatments may remain inaccessible to patients in low- and middle-income countries, further widening global health disparities. Policymakers and stakeholders must therefore ensure affordability and equity remain central to AD nanomedicine development.

Conflict of Interest: The authors declare no conflict of interest.

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